General

Guideline Title

Early detection of prostate cancer: AUA guideline.

Bibliographic Source(s)

Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, Holmberg L, Kantoff P, Konety BR, Murad MH, Penson DF, Zietman AL. Early detection of prostate cancer: AUA guideline. Linthicum (MD): American Urological Association Education and Research, Inc.; 2013 Apr. 28 p. [112 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the body of evidence strength (grade A, B, or C), the strength of the recommendations (Standard, Recommendation, Option), and for statements labeled as Clinical Principle and Expert Opinion are provided at the end of the "Major Recommendations" field.

Age <40 years

Guideline Statement 1. The Panel recommends against prostate-specific antigen (PSA) screening in men under age 40 years. (*Recommendation; Evidence Strength Grade C*)

Age 40 to 54

Guideline Statement 2. The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (*Recommendation; Evidence Strength Grade C*)

Age 55 to 69

Guideline Statement 3. For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in one man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on men's values and preferences. (*Standard; Evidence Strength Grade B*)

Guideline Statement 4. To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening. As compared to annual screening, it is expected that

screening intervals of two years preserve the majority of the benefits and reduce overdiagnosis and false positives. (*Option; Evidence Strength Grade C*)

Age 70+

Guideline Statement 5. The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy. (*Recommendation; Evidence Strength Grade C*)

Definitions:

Rating Scheme for Strength of Evidence

The framework of rating the quality of evidence is an adaptation and modification of the GRADE framework (Grading of Recommendations, Assessment, Development and Evaluation). In this adaptation, the American Urological Association Education and Research, Inc. (AUA) rates the quality of evidence as high, moderate or low (A, B, or C). The confidence in the estimates of effect (quality of the evidence) was determined based on study quality, imprecision, indirectness, inconsistency and the likelihood of reporting and publication bias.

American Urological Association Education and Research, Inc. (AUA) Nomenclature Linking Statement Type to Evidence Strength

Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence

Recommendation: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C evidence

Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A, B, or C evidence

Clinical Principle: A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature

Expert Opinion: A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Prostate cancer

Guideline Category

Prevention

Screening

Clinical Specialty

Internal Medicine

Oncology

Urology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To provide recommendations that are analysis-based or consensus-based for optimal clinical practices in the detection of prostate cancer
- To provide a guideline to address prostate cancer early detection for the purpose of reducing prostate cancer mortality

Note: This document does not address detection of prostate cancer in symptomatic men, where symptoms imply those that could be related to locally advanced or metastatic prostate cancer (e.g., new onset bone pain and/or neurological symptoms involving the lower extremities, etc.)

Target Population

Men at average risk for prostate cancer, defined as a man without risk factors, such as a family history of prostate cancer in multiple generations and/or family history of early onset below age 55 years, or African American race

Interventions and Practices Considered

1. Prostate-specific antigen (PSA) screening in men under age 40 years (not recommended)
2. Routine PSA screening in men between ages 40 to 54 years at average risk (not recommended)
3. Shared decision-making for men age 55 to 69 years that are considering PSA screening
4. Routine PSA screening interval of two years or more versus annual screening
5. Routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy (not recommended)

Major Outcomes Considered

- Prostate cancer incidence
- Mortality
- Quality of life
- The diagnostic performance of each of the tests and the harms of testing (premature death and complications from testing and biopsy)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Consistent with American Urological Association Education and Research, Inc. (AUA) published guideline methodology, the process started by

conducting a comprehensive systematic review. The AUA commissioned an independent group to conduct a systematic review and meta-analysis of the published literature on prostate cancer detection and screening. The protocol of the systematic review was developed *a priori* by the expert panel. The search strategy was developed and executed by reference librarians and methodologists and spanned across multiple databases including Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. Controlled vocabulary supplemented with keywords was used to search for the relevant concepts of prostate cancer, screening and detection. The search focused on digital rectal exam (DRE), serum biomarkers (prostate-specific antigen [PSA], PSA isoforms, PSA kinetics, free PSA, complexed PSA, proPSA, prostate health index, PSA velocity, PSA doubling time), urine biomarkers (PCA3, TMPRSS2:ERG fusion), imaging (transrectal ultrasonography [TRUS], magnetic resonance imaging [MRI], magnetic resonance spectroscopy [MRS], magnetic resonance [MR]-TRUS fusion), genetics (single nucleotide polymorphisms [SNPs]), shared-decision making, and prostate biopsy. The expert panel manually identified additional references that met the same search criteria to supplement the electronic search.

The outcomes of interest were also *a priori* determined by the Panel and included prostate cancer incidence, mortality, quality of life, the diagnostic performance of each of the tests, and the harms of testing (premature death and complications from testing and biopsy). Modeling studies were included when original studies were limited by follow-up time and screening protocols. The methodology team independently rated the methodological quality of the studies and provided an overall judgment of the whole body of evidence based on their confidence in the available estimates of effect.

Number of Source Documents

The systematic review included over 300 eligible studies that addressed the questions of interest.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

The framework of rating the quality of evidence is an adaptation and modification of the GRADE framework (Grading of Recommendations, Assessment, Development and Evaluation). In this adaptation, the American Urological Association Education and Research, Inc. (AUA) rates the quality of evidence as high, moderate or low (A, B, or C). The confidence in the estimates of effect (quality of the evidence) was determined based on study quality, imprecision, indirectness, inconsistency and the likelihood of reporting and publication bias.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The methodology team summarized the data with an explicit description of study characteristics, methodological quality, main findings, and the quality of the evidence (confidence in the estimates). The methodology team attended panel meetings and facilitated incorporation of the evidence into the guideline.

Interpretation of the Evidence

The American Urological Association Education and Research, Inc. (AUA) guideline panel interpretation of the evidence differs from that of a public health perspective. The AUA guideline panel interpreted the evidence from the perspective of the individual with emphasis on the information – both benefit and harm - that an asymptomatic man would need to make an informed decision about prostate cancer screening. The Panel evaluated the best evidence from randomized trials of screening, but did not assume that all trials were of equal relevance. Furthermore, the

Panel utilized population data as supporting evidence for a beneficial effect of screening, and used modeling studies to fill gaps in knowledge. This use of modeling was felt to be important given the short time horizon of a decade provided by current randomized trial results, and the paucity of data regarding the benefits of screening outside the age range of 55 to 69 years.

Quality of Individual Studies and Determination of Evidence Strength

The systematic review included over 300 eligible studies that addressed the questions of interest. In brief, six well known randomized trials addressed the question of mortality benefit of prostate cancer screening. Considering various methodological limitations and biases, the estimate for the effect of screening (versus no screening) on prostate cancer-specific mortality was obtained from the European Randomized Study of screening for Prostate Cancer (ERSPC). The quality of the evidence was moderate for benefits and high for harms in men aged 55 to 69 (see discussion of randomized controlled trials in the original guideline document). Follow-up was quite limited, and quality of evidence was low on screening benefits in men outside of this age range, population subgroups with greater than average risk of the disease and screening protocols different from those used in the ERSPC.

Modeling studies were considered by the Panel to address these issues. A modeling study considers disease progression as a process of clinical or prognostic states and aims to estimate the rates of progression through these states in the absence of screening. Given the rate estimates, different screening protocols can be superimposed and their tradeoffs projected via computer simulation. To validate the models, specific screening protocols used in published studies can be considered and the model-projected incidence patterns compared with those observed in these studies. The primary model considered by the Panel has been validated against prostate cancer incidence trends in the US population before and after the advent of screening and against prostate cancer diagnosis patterns in the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial. Modeling studies are increasingly being used to guide screening policies. The US Preventive Services Task Force used modeling in developing its most recent breast and colorectal cancer screening recommendations.

The evidence concerning harms and adverse effects of screening was high quality, and fairly robust estimates of the incidence of these complications were obtained from randomized and non-randomized studies.

Ample evidence was available to support the use of various shared-decision making processes that increased men's knowledge scores, reduced their decisional conflict, and promoted greater involvement in decision making.

Unfortunately, the literature supporting the efficacy of digital rectal exam (DRE) and biomarkers other than prostate-specific antigen (PSA) for screening average risk men provided minimal evidence to draw conclusions. For the most part, this evidence had low to moderate quality and was more relevant to cancer detection in higher risk men than true average risk population screening. The outcomes of these studies were often reported as diagnostic accuracy estimates rather than patient important outcomes such as mortality or quality of life.

Limitations of the Literature

The systematic review and guideline process identified clear gaps in the available evidence base. Data are needed to clarify the harm/benefit balance of screening in men younger and older than those enrolled in the available randomized trials. Even for the age groups enrolled, critical outcomes, such as overdiagnosis and the additional number needed to treat, are not easily estimated from empirical trial data. Data on the harm-benefit balance are needed in men with varying spectra of family history of prostate cancer and men from various ethnicities and with other known risk factors of developing the disease. Outcomes of newer screening tests used in combination with PSA need to be determined. Men contemplating screening will need outcome data based on follow-up that exceeds the 10 year horizon currently available in the literature.

Extrapolating results from one population to another must be done cautiously since the benefits of screening are dependent on the baseline incidence of and mortality from cancer without screening, the specific screening protocol, biopsy referral criteria and compliance with biopsy recommendations. The mortality from prostate cancer in the absence of screening is higher in the Netherlands and Sweden as compared to the US and these were the only two countries of the seven participating in the ERSPC trial where a mortality benefit was observed. Thus, the benefits of PSA-based screening seen in these two countries may not be generalizable to the US population. Further, the screening protocol, criteria for biopsy referral and compliance with biopsy recommendations differed considerably in the US population and ERSPC trial settings.

Methods Used to Formulate the Recommendations

Expert Consensus

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

This document was written by the Detection of Prostate Cancer Guidelines Panel of the American Urological Association Education and Research, Inc. (AUA), which was created in 2011. The Practice Guidelines Committee of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the committee included urologists, primary care physicians, radiation and medical oncologists, and epidemiologists. Panel members were predominantly urologists. The mission of the committee was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the detection of prostate cancer.

It is important to note that the guideline statements listed in this document target men at average risk, defined as a man without risk factors, such as a family history of prostate cancer in multiple generations and/or family history of early onset below age 55 years, or African American race. Because the harm-benefit profile of prostate-specific antigen (PSA)-based prostate cancer screening is highly age dependent, guideline statements included in this document target four index patients; these age ranges were chosen to correspond to age ranges tested in randomized trials and data from population and simulation studies.

Four index patients:

1. Men <40 years of age
2. Men age 40-54 years
3. Men age 55-69 years
4. Men age 70+ years

The Panel focused on both shared decision making in the face of uncertainty and approaches to early detection of prostate cancer that would reduce harms while maintaining the benefits.

Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens (see the "Rating Scheme for the Strength of the Recommendations" field).

For some clinical issues, little or no evidence may exist from which evidence-based statements can be constructed. In such instances, the Panel may provide guidance in the form of *Clinical Principles* or *Expert Opinions* with consensus achieved using a modified Delphi technique if differences of opinion exist among Panel members. A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge and judgment and for which there is no evidence. In the case of this guideline, such statement types were not included.

Rating Scheme for the Strength of the Recommendations

American Urological Association (AUA) Nomenclature Linking Statement Type to Evidence Strength

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Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The American Urological Association Education and Research, Inc. (AUA) conducted an extensive peer review process. The initial draft of this Guideline was distributed to 52 peer reviewers; 25 responded with comments. The Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the Guideline was submitted for approval to the Practice Guidelines Committee. It was then submitted to the AUA Board of Directors for final approval. The Guideline was approved by the AUA Board of Directors in April 2013.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendation" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate use of prostate cancer screening
- An approach to prostate-specific antigen (PSA) based prostate cancer screening has to take into account the controversies surrounding available data and the fact that over a decade the benefits are modest in terms of prostate cancer deaths averted; 1 death per 1,000 men screened in the European Randomized Study of screening for Prostate Cancer. However the relative benefit (20% reduction in disease-specific deaths) could be very meaningful at the population level. The potential benefits of screening could extend beyond survival as a primary outcome, and will depend on the relevant time horizon for an individual. Further, disconnecting screening from automatic treatment will significantly impact the risk benefit ratio.

Refer to the "Benefits of PSA Screening" section in the original guideline document for additional discussion.

Potential Harms

Harms from Screening

- Prostate cancer screening itself is associated with a number of potential harms, both psychological and physical.
- The transrectal or transperineal prostate biopsy has risks of hematuria, hematochezia, hematospermia, dysuria and retention, pain, and infection. Hematuria and hematospermia are the most frequently observed side effects with wide variation in observed rates. Hematospermia after biopsy occurs in 10% to 70% of patients while hematuria is seen 14% to 50% of the time. While the risk of hospitalization due to bleeding complications remains low, infectious complications are increasing steadily over time, possibly due to fluoroquinolone resistance. The 30-day risk of hospitalization after biopsy for any cause has been estimated to be approximately 4%, of which three in four are for infections. The use of routine fecal culture and sensitivity tailored antibiotic prophylaxis may be one approach to reduce infection rates.
- The American Urological Association Education and Research, Inc. (AUA) has published a white paper to provide some guidance regarding periprocedural prophylaxis. Since prostate biopsies are also an important part of some active surveillance programs, understanding these risks and communicating them to patients is not only integral to informed consent for prostate cancer screening but also for consideration of treatment options.
- Once diagnosed with prostate cancer, a man is faced with the risk of overtreatment of indolent disease due to the assumption that diagnosis with a malignancy must necessarily result in treatment of this malignancy. Estimates of overdiagnosis vary widely from less than 5% to more

than 75% depending upon the population used with lead times of 5 to 15 years.
- Although prostate cancer specific mortality and the need for related palliative care is decreased by screening, quality of life may be impaired as a result due to lasting impairment in urinary, bowel, and sexual function.
- There is considerable distress involved in the decision making process, the biopsy, and deciding among treatment options. Along with the stress due to prostate-specific antigen (PSA) screening and unnecessary biopsies, the diagnosis of prostate cancer alone may incite severe psychological stress with one study showing an increased rate of suicide and cardiovascular events in newly diagnosed men.
- Even when men select active surveillance rather than curative therapy, anxiety may continue and trigger intervention in men who would never have needed treatment in their lifetime; although it would appear that anxiety remains low for most men on surveillance in the short term.

Refer to the "Harms" section in the original guideline document for additional discussion.

Qualifying Statements

Qualifying Statements

- While these guidelines do not necessarily establish the standard of care, American Urological Association Education and Research, Inc. (AUA) seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.
- Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions, and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances.
- Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices. For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, Holmberg L, Kantoff P, Konety BR, Murad MH, Penson DF, Zietman AL. Early detection of prostate cancer: AUA guideline. Linthicum (MD): American Urological Association Education and Research, Inc.; 2013 Apr. 28 p. [112 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Apr

Guideline Developer(s)

American Urological Association Education and Research, Inc. - Medical Specialty Society

Source(s) of Funding

American Urological Association, Education and Research, Inc. (AUA)

Guideline Committee

Detection of Prostate Cancer Guidelines Panel

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Financial Disclosures/Conflicts of Interest

Conflict of Interest Disclosures

All panel members completed conflict of interest disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

Board Member, Officer, Trustee: Philip Kantoff, BIND Biosciences (C) (Expired)

Consultant/Advisor: Peter C. Albertsen, Blue Cross/Blue Shield (C), Dendreon Corporation (C); Glaxo Smith Kline (C) (Expired), Johnson & Johnson (C) (Expired); Stephen J. Freedland, Amgen (C), Medivation (C), Bayer (C), Mitomics (C), Astellas (C), AstraZeneca (C), Dendreon

(C), Janssen (C), Glaxo Smith Kline (C) (Expired); Philip Kantoff, Bellicum (C), BIND Biosciences (C), Blend (C), BN-IT (C), Dendreon (C), Dendreon (C), Johnson and Johnson (C), Metamark (C), Oncocellmdx (C), Sanofi (C), Sotio (C), Tokai (C), Amgen (C) (Expired), Genentech (C) (Expired); Badrinath R. Konety, Allergan (C), Axogen Inc.(U), Dendreon (C), Endo Pharmaceuticals (C), Spectrum Pharmaceuticals (C), Centocor Ortho Biotech (C) (Expired)

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Leadership Position: Anthony L. Zietman, American Board of Radiology (U), American Society for Radiation Oncology (U), National Cancer Institute, GU Steering Committee (C)

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Scientific Study or Trial: Peter C. Albertsen, Agency Health Care Quality (C); Stephen J. Freedland, Glaxo Smith Kline

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the American Urological Association, Inc. (AUA) Web site .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 26, 2013. The information was verified by the guideline developer on August 6, 2013.

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